

REMARKS

Applicants have canceled claims 27-34. Applicants maintain that the cancellation of a claim makes no admission as to its patentability and reserve the right to pursue the subject matter of the cancelled claim in this or any other patent application.

Claims 18 and 35 were amended to recite "a pharmaceutical composition comprising zonisamide, or a pharmaceutically acceptable salt thereof." Support for this amendment can be found throughout the application as filed, for example, at page 5, second paragraph.

Claims 25 and 42 are amended to recite "wherein said pharmaceutical composition is administered in combination with a reduced calorie diet or increased physical activity." Support for these amendments can be found throughout the application as filed, for example, at page 12, first full paragraph.

Claim 35 is amended to recite "wherein the weight loss is $\geq 5\%$, or wherein said weight loss continues during the period of administration of said composition comprising zonisamide or a pharmaceutically acceptable salt thereof." Support for these amendments can be found throughout the application as filed, for example, at Figure 2, and pages 19-20.

Support for new claims 44-52 can be found throughout the specification as filed, including the original claims. Applicants submit that no new matter was added by the amendments to the claims. Claims 18-26 and 35-52 are presented for examination. For the reasons discussed below, Applicants respectfully traverse the pending rejections.

35 U.S.C. § 112, Second Paragraph – Indefiniteness

Claims 18-43 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. In particular, the Examiner objects to the recitation of the phrase "significant" and "sustained" in claims 18 and 35, and "a hypocaloric diet" and "exercise" in claims 25 and 42. Applicants respectfully traverse.

Applicants submit that the objected to terms do not render the claims indefinite as they have well-established meanings. However, in the interest of advancing prosecution, Applicants have amended claims 18, 25, 35 and 42 to delete the objected to terms. Claims 25 and 42 are amended to recite "wherein said pharmaceutical composition is administered in combination with a reduced calorie diet or increased physical activity." Claim 35 is amended

to recite “wherein the weight loss is $\geq 5\%$, or wherein said weight loss continues during the period of administration of said composition comprising zonisamide or a pharmaceutically acceptable salt thereof.”

Applicants respectfully submit that the pending claims are sufficiently definite, and therefore request that the Examiner reconsider and withdraw the rejection of the pending claims under 35 U.S.C. § 112, second paragraph.

35 U.S.C. § 112, First Paragraph – Scope of Enablement

Claims 27-34 are rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. The Examiner argues that, while enabling for reducing weight in an overweight patient, the specification “does not reasonably provide enablement for treating eating disorders in a subject.” *Office Action* at 5-6. Applicants respectfully traverse.

While Applicants do not acquiesce to the Examiner’s rejection, in the interest of furthering prosecution, Applicants have canceled claims 27-34, rendering the rejection moot.

35 U.S.C. § 102(e) - Anticipation

The Examiner has rejected pending claims 18-43 under 35 U.S.C. § 102(e) as being anticipated by Jennings (US 2004/0029941).

Applicants note that in a Submission mailed April 23, 2004, Applicants requested that the Office declare an interference between the instant application and Jennings.

Applicants maintain that Jennings is not a proper 35 U.S.C. § 102(e) reference since Applicants can swear behind the reference, and therefore Jennings was not filed prior to invention of the instant subject matter by Applicants. Applicants note that Jennings earliest priority date is only eleven days earlier than Applicants’. Applicants will consider submitting a declaration to this effect pursuant to 37 C.F.R. § 1.131 at the Examiner’s request.

Rejections under 35 U.S.C. § 103(a)

Ayala et al.

Claims 18-21 and 35-38 are rejected under 35 U.S.C. § 103(a) over Ayala. The Examiner argues that Ayala teaches that “the administration of zonisamide is effective in

decreasing weight loss in patients,” that “[f]ifteen of the 23 patients experienced a weight loss of 4-11% of total body weight,” and that “[t]here patients had weight loss of greater than 10%.” *Office Action* at 10-11. The Examiner states that while Ayala does not teach that the weight loss was significant and sustained for treating overweight subjects, “since the observations disclosed in Ayala show that zonisamide is associated with weight loss in epileptic patients,” one of skill in the art would have been motivated to administer zonisamide to an overweight patient with a reasonable expectation of success. *Id.* at 11.

Claims 22-23 and 39-40 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Ayala in view of Shank. The Examiner states that while Ayala does not disclose oral administration of zonisamide, determination of the appropriate route of administration is routine, and Shank “discloses anticonvulsant derivatives such as topiramate useful in treating obesity where the active ingredient topiramate is prepared for oral administration.” *Office Action* at 11-12. The Examiner therefore concludes that oral administration of zonisamide is obvious. Applicants respectfully traverse.

Ayala does not disclose or suggest that zonisamide would be useful when intentionally administered to (i) treat obesity in a patient having a BMI of 30 kg/m² or more; (ii) treat obesity or reduce weight in an obese or overweight patient; or (iii) produce significant (e.g., at least 5%) and/or sustained weight loss in a patient.

Ayala describes the adverse effects of administering zonisamide to 23 epileptic patients. Ayala notes that “drug-related weight loss is considered to be an adverse event” and that “in patients already below their ideal weights a further loss of 10% may be a problem.” Ayala does not disclose or suggest any relationship between initial body weight in epileptic patients and weight loss in the 23 epileptic patients studied, nor does Ayala indicate that any epileptic patients in the study were obese or overweight.

The Examiner asserts that Ayala reports that 15 of 23 patients experienced weight loss of 4-11 %. The Examiner, however, fails to mention the following facts described in Ayala:

- (i) of the patients who experienced weight loss, 2 patients returned to their baseline weight by the conclusion of the study;
- (ii) 2 patients had a weight loss of only 1 %;
- (iii) 1 patient did not have any change in weight; and

(iv) 5 patients experienced weight gains of 1-3.5%.

Only 23 epileptic patients were in the study, and of those only 13 patients received zonisamide for a period longer than 14 months. The remaining 10 patients received zonisamide from 2 to less than 14 months. Moreover, Ayala reports that no statistical analysis was performed.

The FDA Approved Labeling Text (submitted herewith as Exhibit 1) for zonisamide reports that only 1% (3 of 269) of epileptic patients in controlled clinical trials experienced weight loss as an adverse event compared 2 of 230 placebo patients. *See FDA Approved Labeling Text* at 14 and 16. One skilled in the art would not expect the adverse event of weight loss that occurred in only 1% of epileptic patients in controlled clinical trials to provide any suggestion, motivation, or reasonable expectation of success to use zonisamide for weight loss in obese or overweight patients of the general population (i.e., non-epileptic patients). Moreover, there is no statement in the FDA Approved Labeling Text of how many epileptic patients in the study were obese or overweight and how many of the obese or overweight epileptic patients experienced the adverse event of weight loss. *Id.* at 14. Finally, Applicants note that weight gain is also listed as a reported adverse event. *Id.* at 18.

When viewing the teachings in Ayala and the FDA Approved Labeling Text for zonisamide, one of ordinary skill in the art would consider the teachings in the FDA Approved Labeling Text to definitively discredit the teachings in Ayala. One skilled in the art would believe the results in an FDA-approved, controlled clinical trial when compared to Ayala's uncontrolled study involving only 23 patients. *See MPEP 2143.01, Part II.* Ayala does not provide motivation or a reasonable expectation of success for using zonisamide to promote weight loss in obese or overweight patients when viewed in light of the FDA Approved Labeling Text which teaches that only 1% of the patients in the FDA-approved, controlled clinical trial experienced weight loss when using zonisamide, a nearly equal amount of placebo patients also reported weight loss, and weight gain is also reported as an adverse event.

One of ordinary skill in the art would conclude that zonisamide would not be useful or successful in weight loss and would not be motivated to use zonisamide for reducing weight in obese or overweight patients in view of the teachings in the FDA Approved

Labeling Text. One skilled in the art would dismiss the teachings in Ayala as being discredited by the results of the FDA-approved, controlled clinical trial described in the FDA Approved Labeling Text for zonisamide.

In view of the above, Applicant respectfully submits that Ayala, alone or in combination with Shank, does not render the pending claims obvious, and respectfully requests that the rejection under 35 use § 103(a) over Ayala be withdrawn.

Coffin et al.

Claims 18-26 and 35-43 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Coffin in view of Shank and Anderson. The Examiner states that Coffin teaches a method for reducing food cravings by administering a compound of D₁/D₅ antagonist or partial agonist with an anticonvulsant, where the anticonvulsant can be zonisamide, and therefore Coffin discloses a composition comprising zonisamide. The Examiner asserts that:

In looking at the whole context of Coffin et al.'s disclosure, Coffin et al.'s treatment for reducing cravings to food is directed to treating obesity (page 1, left column, lines 6; page 3, Example 4; and page 4, Example 6) and therefore is directing to a method of reducing weight in an overweight subject. Therefore, Coffin et al.'s disclosure provides the skilled artisan with the necessary motivation and guidance to treat obesity or reduce weight gain in an individual in need thereof by reducing cravings for food in the individual. *Office Action* at 13.

In combination with Coffin, the Examiner cites Andersen as disclosing a method of treating obesity by administration of a compound in combination with a hypocaloric diet or exercise, and Shank as disclosing topiramate as useful for treating obesity. *Office Action* at 14.

It appears that the Examiner has take the position that because Coffin discloses treating food cravings with a D₁/D₅ antagonists/partial agonists, optionally in combination with a laundry list of over 100 other compounds including zonisamide, one of skill in the art would be motivated to use a composition comprising zonisamide to treat obesity. The Examiner reaches this conclusion based on the assertion that Coffin's treatment of food cravings is "directed to treating obesity."

Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness based on Coffin for at least two reasons. First, Applicants respectfully submit that the disclosure of the use of D₁/D₅ antagonists/partial agonists for the treatment of food cravings does not suggest the administration of compositions containing zonisamide as a method of reducing weight or treating obesity in an overweight subject. Reading Coffin, one of skill in the art would not be motivated to use compositions containing zonisamide to treat food cravings, or obesity. Second, even if such motivation existed, there is no reasonable likelihood of success, since Coffin does not provide any examples of treating obesity using compositions containing zonisamide.

To begin with, Applicants note that elsewhere in the Office Action, the Examiner expresses the opinion that treating obesity is not the same as treating eating disorders, such as food cravings. The Examiner states:

The [instant] specification discloses example studies regarding the effects of weight reduction by administering zonisamide to obese patients. Although obesity may be related to an eating disorder, **a method of treating obesity is not the same as a method of treating an eating disorder.** *Office Action* at 7 (emphasis added).

Second, Applicants note that none of the examples in Coffin utilize a composition containing zonisamide. Coffin merely states that the disclosed D₁/D₅ antagonists/partial agonists may be administered alone or in combination “with other specified CNS compounds” including a long laundry list of compounds (approximately 108 different compounds or classes of compounds), only one of which is zonisamide. *Coffin* at ¶¶[0072]-[0081]. Coffin states that combining the D₁/D₅ antagonists/partial agonists with other CNS compounds “may permit lower doses of each compound to be used thereby providing increased efficacy while decreasing side effects.” *Id.* at ¶[0082].

This statement does not provide one of skill in the art with any motivation to use zonisamide to treat food cravings, yet alone obesity (which the Examiner states “are not the same”). The Examiner has not provided any reason one would select zonisamide from among a list of over 100 compounds and classes of compounds. If one includes all of the compounds in the classes of compounds listed by Coffin (e.g., all antipsychotic drugs, all antidepressants, all anticonvulsants, all mood stabilizers, etc.) the list is likely to include

hundreds of compounds. Given the large laundry list, Applicants respectfully submit that the Examiner is impermissibly using Applicants' disclosure and hindsight to select zonisamide.

Even if Coffin provided a motivation to use compositions containing zonisamide to treat food cravings, Coffin provides no reasonable expectation that zonisamide compositions can be used to successfully treat obesity.

The Examiner cites three portions of Coffin which allegedly connect treating food cravings to treating obesity. The first paragraph cited by the Examiner simply states that considerable research has been directed to obesity, that obesity is costly to society, and that food cravings are difficult to treat. *Coffin* at ¶ [0002]. This does not provide any reasonable likelihood that obesity can be treated by using zonisamide to treat food cravings.

The second portion of Coffin cited by the Examiner is Example 4, where Coffin discloses that treating trained rats with a D₁/D₅ antagonist interfered with the rat's bar pressing for a food reward. This Example implicates D₁/D₅ receptors in the reward pathway, but says nothing about treating obesity, as there was no measure of weight loss. In addition, this example does not use zonisamide.

The Examiner also cites Example 6, which has nothing to do with treating food craving, but instead is a study of using a D₁/D₅ antagonist to treat cocaine addiction, not food cravings. Nowhere does Example 6 state that the cocaine addicts suffered from food cravings, or that their food cravings were treated by the D₁/D₅ antagonist. Thus, Example 6 says absolutely nothing about whether treating food cravings is effective at treating obesity.

Examples 4-6 purport to show that certain D₁/D₅ antagonists may reduce food intake: Example 4 discloses that a D₁/D₅ antagonist reduces food consumption in genetically obese mice; Example 5 discloses that a D₁/D₅ antagonist reduces NPY induced feeding in rats; and Example 6 indicates that a D₁/D₅ antagonist may cause weight loss in some overweight cocaine addicts. However, none of these examples use compositions containing zonisamide. Therefore, they provide no motivation or likelihood of success for using zonisamide compositions to treat obesity – treating cravings with a D₁/D₅ antagonist is not the same as using zonisamide to treat obesity.

For at least the above reasons, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness based on the Coffin reference. Neither of the

Andersen or Shank references cure these deficiencies. Accordingly, Applicants respectfully request withdrawal of the rejection of Claims 18-26 and 35-43 under § 103(a) over Coffin et al., alone or in combination with Andersen and Shank.

Obviousness-type double patenting rejections

Claims 18-43 are rejected under the doctrine of obviousness-type double patenting over claims 1-11 of U.S. Patent No. 7,109,198 (previously copending U.S. Patent App. No. 10/440,404). The Examiner states that while the claims are not identical, they are not patentably distinct “because both the instant invention and copending Application No. 10/440,404 teach of treating obesity and hypertension (and diabetes or dyslipidemia) wit the administration of zonisamide or topiramate along with bupropion.” *Office Action* at 15. Claims 18-43 are provisionally rejected under the doctrine of obviousness-type double patenting over co-pending Application Nos. 11/058,981, 11/059,027, and 11/034,316.

Applicants respectfully request the Examiner to hold the obviousness-type double patenting rejections in abeyance until the prosecution of the present application and the aforementioned co-pending applications have progressed further.

CONCLUSION

In view of the above, Applicants respectfully maintain that claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment, to Deposit Account No. 11-1410.

Respectfully submitted,
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